

# VESICULOBULLOUS DISEASES OF THE NEWBORN



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**Table 2.** Differential Diagnosis of Cutaneous Vesicles, Bullae, and Erosions in the Neonate.

**Infectious vesiculopustular dermatoses**

Herpes simplex virus infection

Varicella infection

Cytomegalovirus

Candida infection

Scabies

Aspergillus infection

Bacterial infection

Group B streptococcus

Group A streptococcus

*Haemophilus influenzae* type B

*Staphylococcus aureus*

Listeria

*Treponema pallidum*

*Pseudomonas*

**Table 2. Differential Diagnosis of Cutaneous Vesicles, Bullae, and Erosions in the Neonate.**

**Noninfectious transient conditions with vesicles and erosions**

Erythema toxicum neonatorum

Transient neonatal pustular melanosis

Miliaria

Neonatal acne

Eosinophilic pustular folliculitis

Acropustulosis of infancy

Sucking blister

Trauma

**Table 2.** Differential Diagnosis of Cutaneous Vesicles, Bullae, and Erosions in the Neonate.

### **Nontransient bullous dermatoses**

Epidermolysis bullosa

Incontinentia pigmenti

Epidermolytic hyperkeratosis

Hyper-IgE syndrome

Herpes gestationis

Pemphigus vulgaris


Langerhans'-cell histiocytosis

Mastocytosis



## A. Infectious Neonatal Vesiculopustular Dermatoses

### 1. *HSV*

- Devastating consequences if not detected and treated
  - Infection in utero transplacental or ascending infection from the maternal genital tract
  - History of recent HSV infection in the mother, but often no
  - 3 forms: mucocutaneous infection, disseminated infection, and infection of the central nervous system
  - Begin as solitary, grouped, or diffuse erythematous macules; within 24 to 48 h vesiculopustules, crusts, erosions
  - Oral involvement is common
  - Skin lesions typically appear days after onset of systemic
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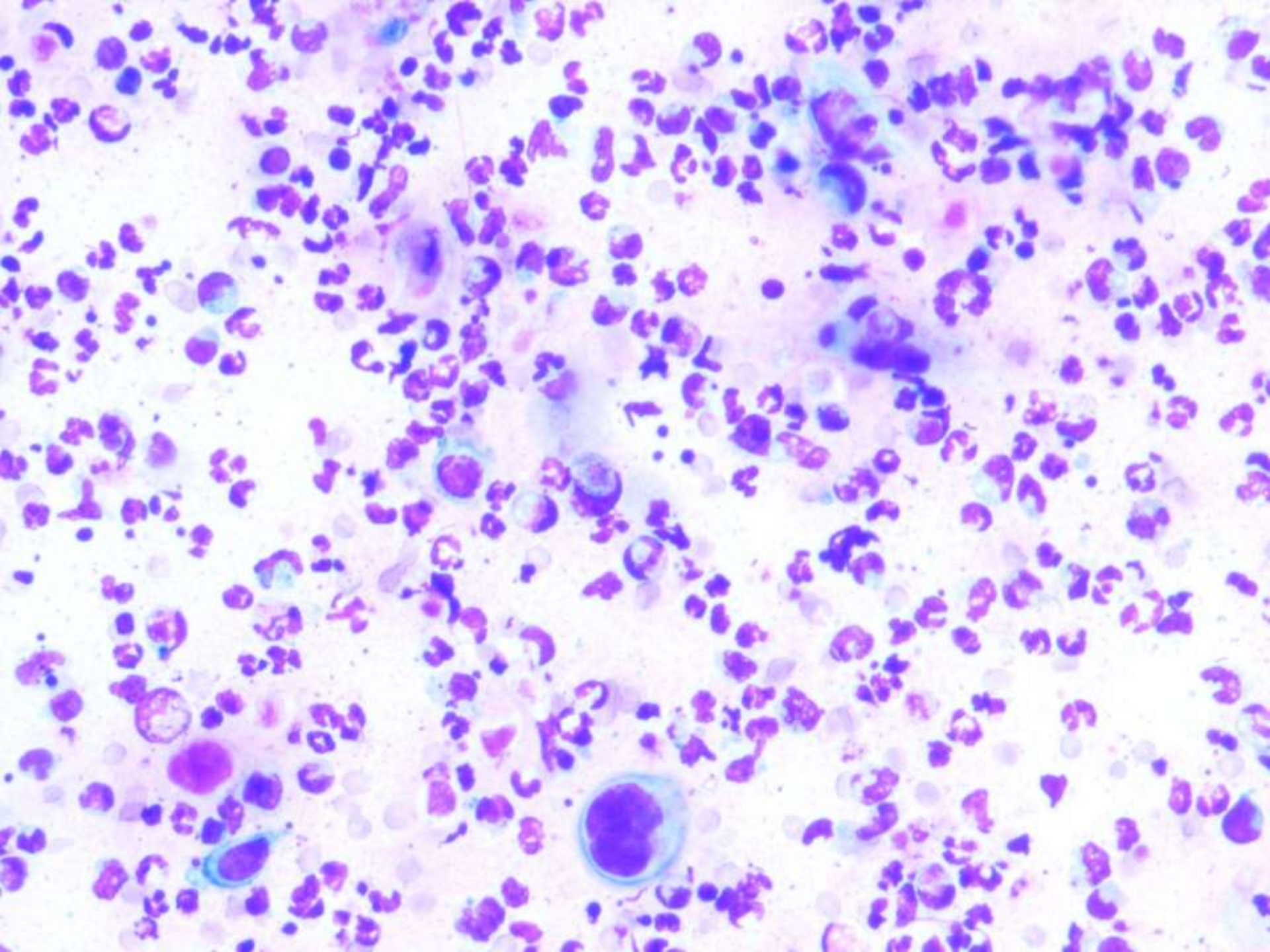




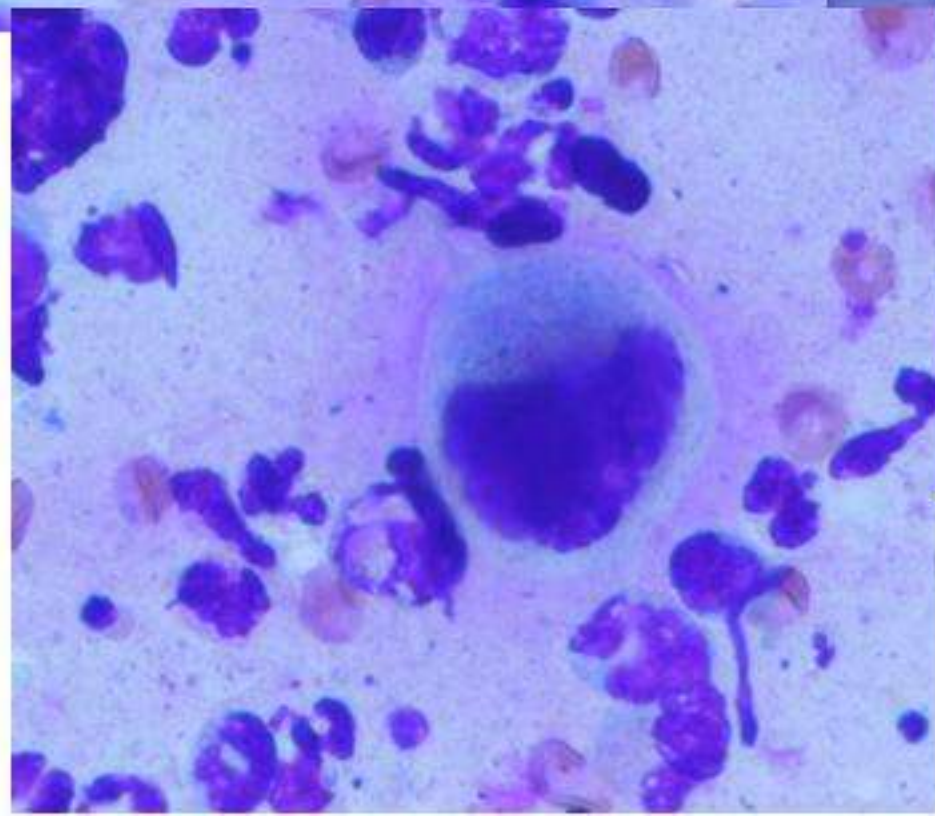
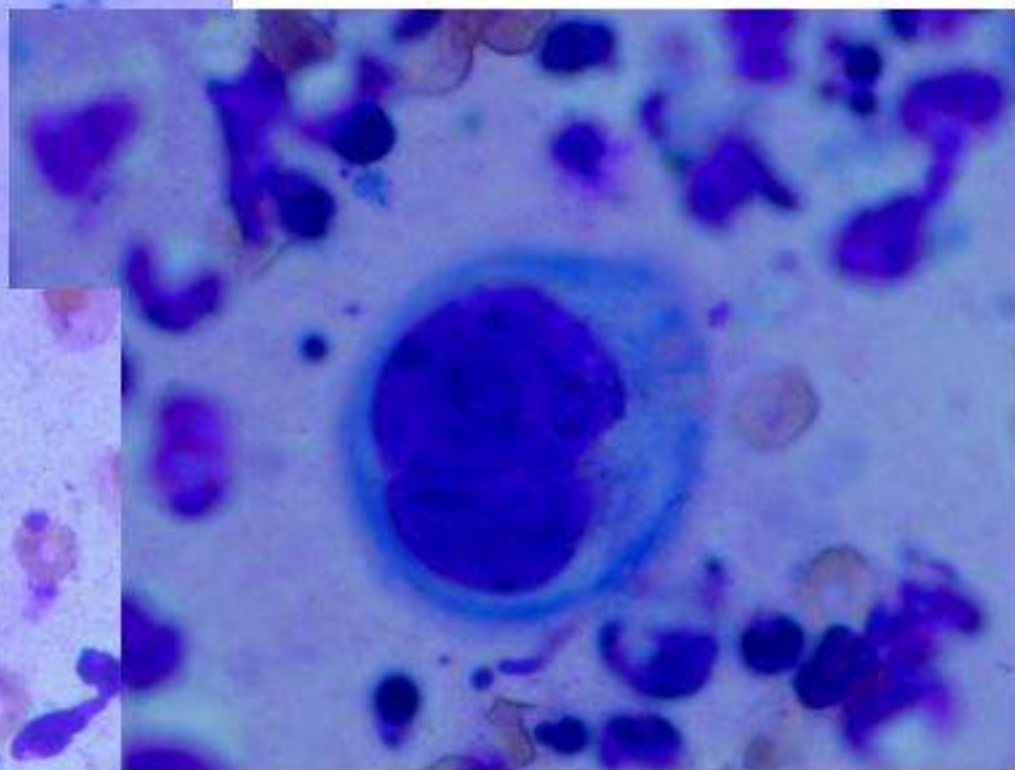
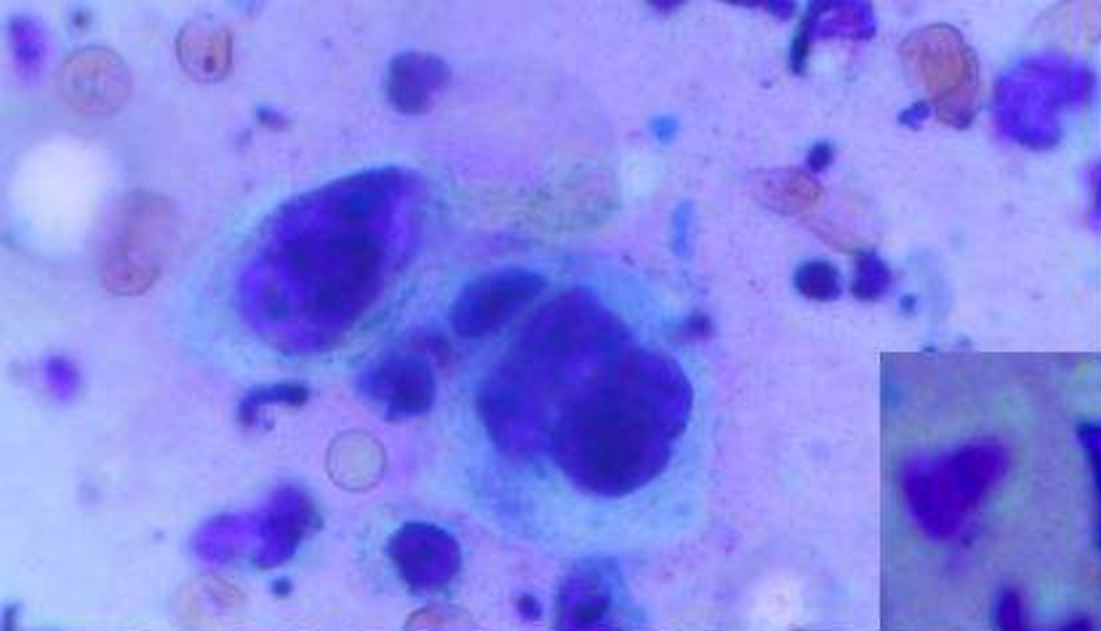


- May also be jaundice; hepatitis; lung, liver, and brain involvement with deterioration of the central nervous system (encephalitis and seizure); sepsis; and CIRD
- If neonatal HSV suspected, IV acyclovir
- Without antiviral therapy, 80% mortality; with TRT, 30%
- Most rapid test = Tzanck; reliability depends on the Physician, and even in skilled hand, accurate in only 67%
- Direct fluorescent antibody test : more accurate, but not available at all hospitals, not 100% sensitive, false positive









- Viral culture of skin, conjunctiva, cerebrospinal fluid, or urine specimens remains the gold standard
- Examination of cerebrospinal fluid samples may show pleocytosis, elevated protein levels, and the presence of red cells
- MRI may show encephalitis within 3 days after birth, whereas findings on CT Scan may not be abnormal until after 5 days



## 2. *Varicella*

- Occur when mother has infection in the last 3 weeks of pregnancy
- Appears in infant 9 to 15 days after the maternal rash develops, administration of varicella–zoster Ig may prolong incubation period to 28 days
- Cutaneous manifestations: pink macules that develop into papules and “teardrop” vesicles, sparse or numerous, necrotic and hemorrhagic in severe cases
- Systemic findings: pneumonitis, respiratory distress, hepatitis, and encephalitis





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### 3. *Cytomegalovirus*

- One of the most common infections of the neonate
- 5 to 10% of infected neonates have symptoms
- Vesicles are rare and present only at birth

*When vesicles are present at birth,  
cytomegalovirus infection must be considered*

- Viral cultures of blood and urine have the highest sensitivity when performed within 1 week after infection
- PCR for CMV DNA in plasma : very sensitive



#### 4. *Candida*

- Most common fungal infection of the neonate
- Congenital candidiasis usually manifests on the first day of life as result of exposure in utero or during delivery or within 1 week if acquired during delivery
- Risk factors: foreign body in the uterus (such as an intrauterine device or a cervical suture), a maternal history of vaginal candidiasis, and premature delivery
- Most cases are mild and confined to the skin
- Generalized eruption of red macules, pustules, vesicles, and vesiculopustules on the first day of life
- Spores and pseudohyphae , KOH preparation of skin scrapings
- Repeated blood, cerebrospinal fluid, and urine cultures if suspected disseminated infection, because initial cultures

## 5. *Bacterial Infection*

- Symptoms of bacterial sepsis — including lethargy, jaundice, purpura, fever, and shock —typical
- Group B streptococcus = most common cause of bacterial sepsis in newborn

Skin : vesicles, bullae, crusts, and erosions, but often systemic manifestations: bacteremia, meningitis, pneumonia



- Impetigo neonatorum : infection with *Staphylococcus aureus* (phage group II, type 55, with 71 subtypes); large, flaccid bullae and moist, sometimes golden-crust ed erosions from impetiginization

Typically, mild eruptions but may be severe and life-threatening, with osteomyelitis, pneumonia, and sepsis.

- Bullae usually appear in the second week of life.
- Staphylococcal scalded skin syndrome begins with a scarlatiniform eruption that rapidly progresses to bullae and desquamation of large portions of skin, resembling toxic epidermolytic necrosis, with a characteristic golden crusting around the mouth and nose.



## ○ *Congenital Syphilis*

- Infected mothers, transplacental transmission
- 40% of infected newborns have skin findings at delivery: papulosquamous eruptions, condylomata lata, and desquamation; more rarely, vesicles and bullae specific to the newborn
- Hemorrhagic bullae on palms and soles
- Serologic tests in the mother during pregnancy and in the neonate, as well as a VDRL test of a cerebrospinal fluid specimen



## Bacterial infection

Group B streptococcus

Group A streptococcus

*Haemophilus influenzae* type B

*Staphylococcus aureus*

Listeria

*Treponema pallidum*

Pseudomonas



*Imperative to treat with AB for bacterial and viral infections until conclusively ruled out*

*Ideally, cultures performed before the broad AB coverage with IV ampicillin, gentamicin, and acyclovir*

*Infants who have vesiculopustular rashes and who appear ill should be tested for Candida, viral, and bacterial infections*



## **B. Noninfectious Conditions in the Neonate with Vesicles and Erosions**

### **1. Erythema toxicum neonatorum:**

- Common in healthy infants
- First week of life
- Erythematous macules, wheals, papules, and pustules that wax and wane, with new lesions persisting for several days
- Begins on the face and migrates to the trunk
- No involvement of palms or soles















**SFS**



A close-up photograph of human skin, likely on the back or chest, showing a vertical crease or fold. Numerous small, white, raised bumps (papules) are scattered across the skin surface, particularly concentrated along the crease and on the right side. The skin has a reddish-pink hue.

**SFS**

## 2. Transient neonatal pustular melanosis :

- Superficial pustules with no erythema
- Rupture easily, scaling
- Hyperpigmented macules with or without scale
- Anywhere on the skin, including the palms and soles
- Resolution within 3 to 4 weeks
- No treatment indicated

















### 3. Acropustulosis of infancy :

- Extremely pruritic
- Vesiculopustular eruption on the hands and feet present at birth or within the first few weeks of life
- Appears every 2 to 4 weeks, persisting for 5 to 10 days during each episode
- Usually resolves in 1 to 2 years and is responsive to topical CS











## **Noninfectious transient conditions with vesicles and erosions**

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Transient neonatal pustular melanosis

Miliaria

Neonatal acne

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Sucking blister

Trauma





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## C. Nontransient Bullous Dermatoses of the Neonate

### ○ Several inherited disorders :

#### i. Epidermolysis bullosa:

- Most affected patients present at birth with vesicles, bullae, and denuded skin and mucous membranes

#### ii. Incontinentia pigmenti :

- Manifestation at birth in about half of all cases
- Linearly arranged vesicles following the lines of Blaschko





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iii. Epidermolytic hyperkeratosis :

- Very rare, AD disorder
- Defects in the genes encoding keratins 1 and 10
- Widespread bullae, erythroderma, and desquamation at birth

iv. The hyper-IgE syndrome (Job's syndrome):

- Solitary or numerous vesicles tense, with surrounding erythema
- Head and shoulders







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- Two autoimmune diseases of the mother can affect neonates:

1. Herpes gestationis

2. Pemphigus vulgaris: maternal autoantibodies can pass transplacentally to the newborn



## ○ Langerhans'-Cell Histiocytosis

- Congenital form = clonal proliferative disorder of Langerhans' cells (= APC derived from bone marrow)
- Single organ or multiorgan-system involvement at birth
- Hashimoto–Pritzker's disease, or congenital self-healing reticulohistiocytosis = one end of the spectrum of single-organ–system LH, high likelihood of complete, sp. resolution
- Skin lesions : solitary or multiple vesicles, bullae, erosions, papules, nodules, crusts, petechiae, milia, and atrophy. Erosions have more poorly defined borders than those of neonatal herpes
- Tzanck preparation: characteristic reniform nuclei and abundant cytoplasm
- Skin biopsy for a definitive diagnosis







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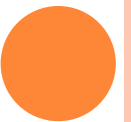


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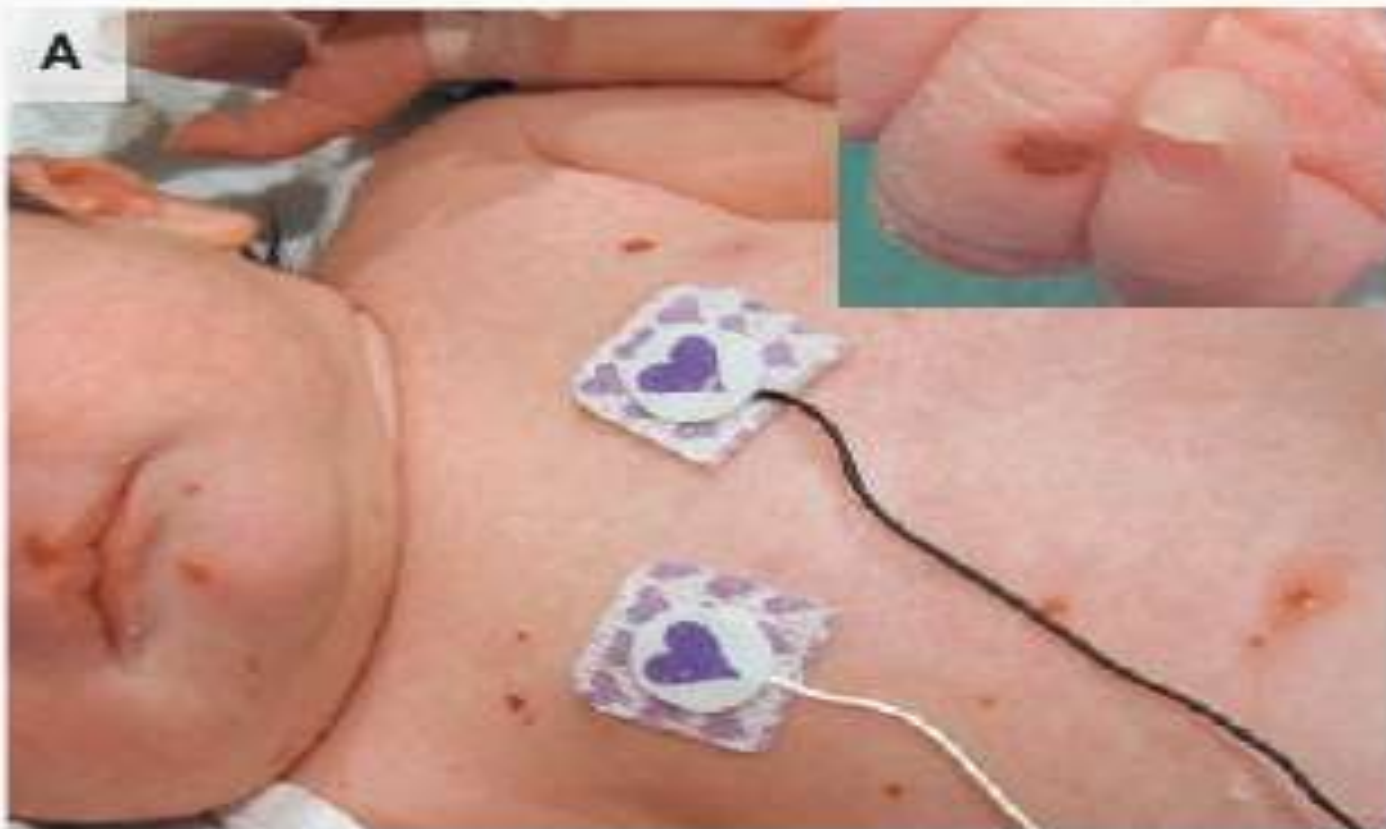
# CLINICAL CASE

- Newborn girl
- Weight = 3105 g, spontaneous vaginal delivery at 40 weeks' gestation
- Healthy 27-year old mother after an uncomplicated pregnancy
- Numerous pustules on the face, trunk, arms, and legs
- Mother: no exposures to infectious diseases, genital infections, or rashes during the pregnancy ;
- Tests for antibodies to rubella and HSV were positive
- Tests for antibodies to syphilis and hepatitis B were negative
- Rectovaginal culture : positive for group B streptococcus
- Mother had varicella infection in childhood
- No medications and no illicit drugs, alcohol, or tobacco
- Rupture of membranes 2 hours before vaginal delivery, and AB administered IV during delivery
- Tzanck smear : positive for multinucleated giant cells
- Lumbar puncture attempted three times but unsuccessful



- On examination: temperature = 36.8°C, pulse = 135 beats per minute, blood pressure = 74/58 mm Hg, SaO<sub>2</sub> = 99%; 56 breaths per minute
- 50 cutaneous erosions and papules, 3 to 7 mm in diameter with serosanguineous crust, surrounding pink erythema; over the scalp, face, trunk, arms, and legs
- No involvement of groin area or oral, conjunctival, or vaginal mucosae
- No dysmorphic features
- Mucous membranes were pink and moist, palate intact
- Neck was supple
- Auscultation of the heart and lungs : nl
- No enlarged lymph nodes in the cervical, axillary, or inguinal regions
- Hepatomegaly?
- Genitalia normal
- Neurologic examination normal







**Table 1. Results of Laboratory Tests.\***

Variable	Age-Adjusted Reference Range or Value†	Value in Our Patient
Hematocrit (%)	42.0–60.0	32.8
Hemoglobin (g/dl)	13.5–19.5	11.1
White-cell count (per mm <sup>3</sup> )	For birth to 24 hours of age, 9000–30,000 For 1–7 days of age, 9400–34,000	17,800
Neutrophils (%)	For birth to 24 hours of age, 66–87 For 1–7 days of age, 53–62	41
Lymphocytes (%)	For birth to 24 hours of age, 22–37 For 1–7 days of age, 21–34	37
Atypical lymphocytes (%)	0	2
Monocytes (%)	4–11	3
Band forms (%)	<10	15
Eosinophils (%)	0–8	1
Platelet count (per mm <sup>3</sup> )	150,000–450,000	180,000
Mean corpuscular volume (fl)	98–118	108
Coagulation test results		
Prothrombin time (sec)	10.1–15.4	13.4
Partial-thromboplastin time (sec)	25.3–48.3	23.7
Sodium (mmol/liter)	135–145	139
Potassium (mmol/liter)	4.0–5.6	4.4
Chloride (mmol/liter)	98–106	104
Carbon dioxide (mmol/liter)	19.0–22.0	20.6
Glucose (mg/dl)	60–100	71
Total protein (g/dl)	6.0–8.3	5.4

**Table 1.** (Continued.)

Variable	Age-Adjusted Reference Range or Value†	Value in Our Patient
Magnesium (mEq/L)	1.4–2.0	1.3
Urea nitrogen (mg/dl)	5–20	5
Creatinine (mg/dl)	0.3–1.0	0.5
Calcium (mg/dl)	8.5–10.5	7.3
Aspartate aminotransferase (U/liter)	47–150	62
Alanine aminotransferase (U/liter)	7–30	34
Bilirubin (mg/dl)		
Direct	0.5–3.5	0.5
Total	2.0–15.0	1.3
Alkaline phosphatase (U/liter)	15–350	81
Lactate dehydrogenase (U/liter)	110–210	646
Lipase (U/dl)	1.3–6.0	1.2
Cerebrospinal fluid results		
Red-cell count (per mm <sup>3</sup> )	None	115,000
White-cell count (per mm <sup>3</sup> )	0–30	222
Neutrophils (%)	0	86
Band forms (%)	0	4
Lymphocytes (%)	0	3
Monocytes (%)	0	5
Eosinophils (%)	0	2
Glucose (mg/dl)	50–75	31
Protein (mg/dl)	5–55	133

- Scrapings from several skin lesions : no neutrophils or organisms identified, cultures negative
- IFD assays for HSV and the VZV: negative
- Viral cultures, fungal staining, and fungal cultures: negative
- Cultures of rectal, conjunctival, and nasopharyngeal swab specimens were negative for HSV
- Blood cultures, urine cytomegalovirus shell-vial culture, and rapid plasma reagin tests : negative
- Cerebrospinal fluid specimen : no organisms, VDRL and HSV amplification negative
- MRI of the brain: nonspecific finding
- Abdominal ultrasonography : borderline hepatomegaly without focal infiltration of the parenchyma



- Rash at birth without systemic symptoms decreased suspicion for HSV infection; in addition, no oral or mucosal lesions were present
- Mother reported a history of childhood varicella infection and had no recent evidence of illness, making this diagnosis unlikely, and testing for this virus in the infant was negative
- Urine culture for CMV in this case was negative
- Newborn had no apparent distress, and smears and cultures showed no evidence of candidiasis, no thrush





- Well-appearing infant → bacterial sepsis unlikely, and appropriate bacterial cultures of specimens from the lesion, blood, urine, and cerebrospinal fluid were negative
- Although likelihood of a serious bacterial infection or sepsis was low in this infant, it was imperative to treat her with AB for bacterial and viral infections until they were conclusively ruled out. Then investigation for noninfectious causes of vesiculopustular eruptions

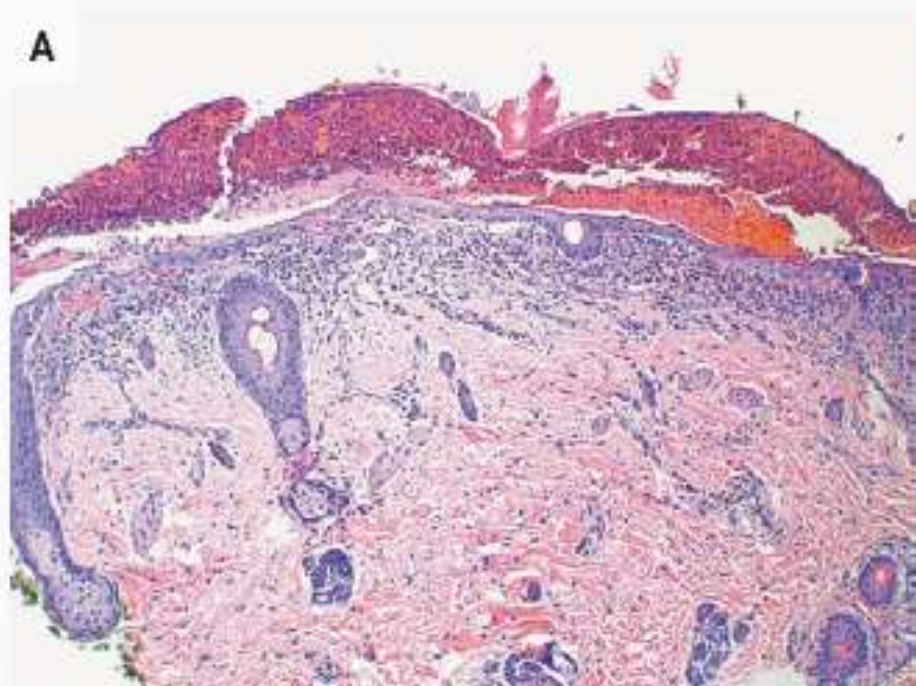
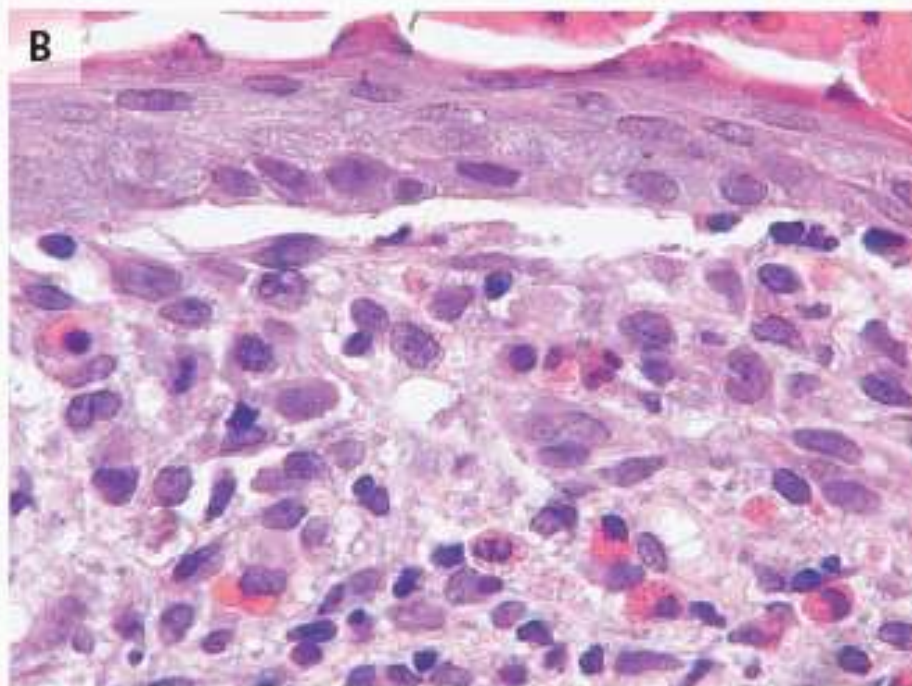
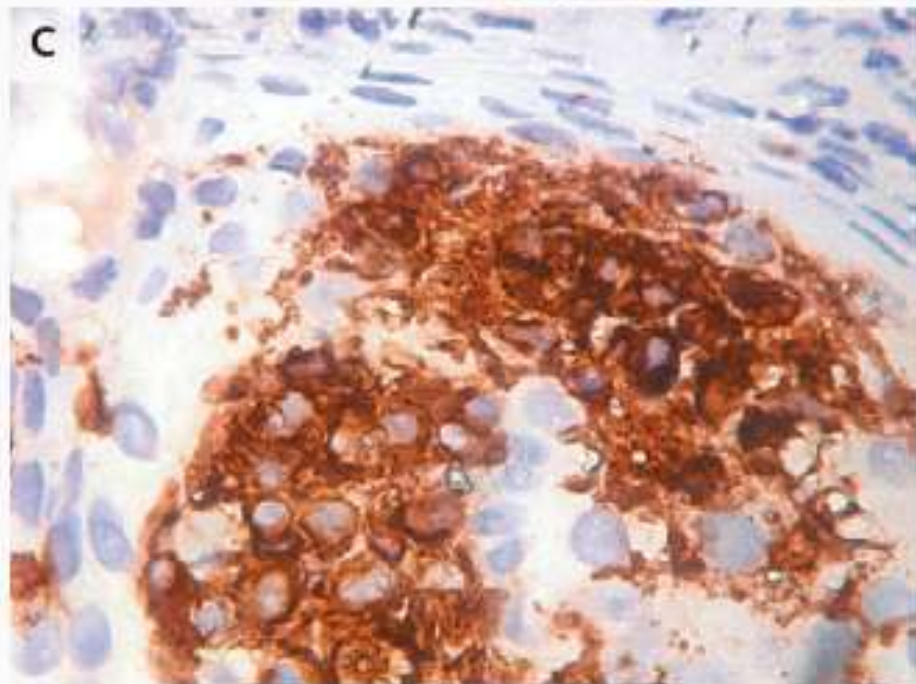
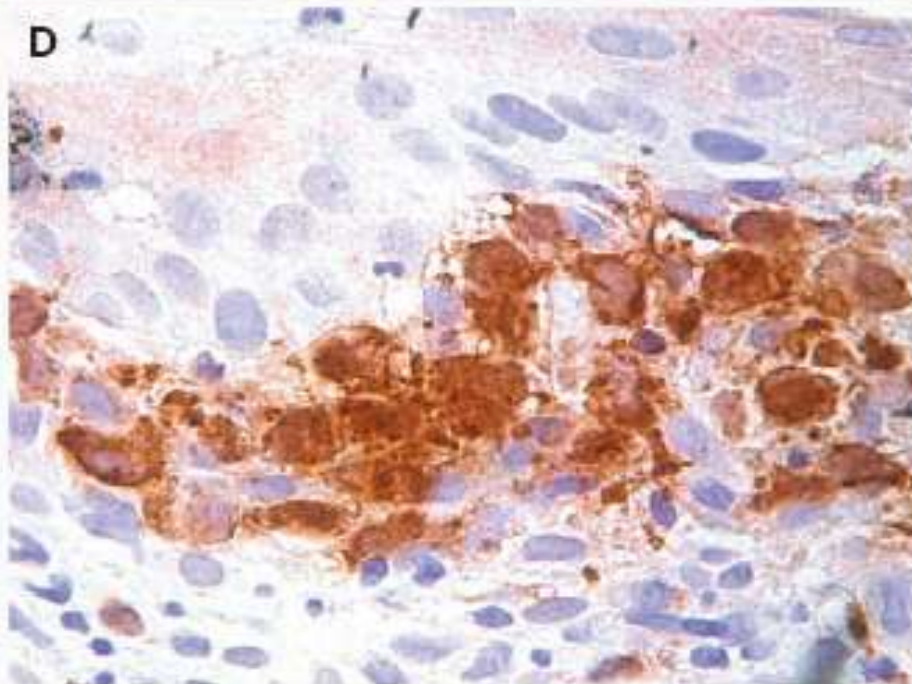


- None of the benign transient dermatoses resembled the presentation of this newborn
- Epidermolysis bullosa, Incontinentia pigmenti, Epidermolytic hyperkeratosis, hyper-IgE syndrome: none of these disorders appeared likely in this patient with no family history
- Herpes gestationis, pemphigus vulgaris: the mother had no history of either of these disorders



- Biopsy of a lesion on the flank



**A****B****C****D**



- Epidermal ulceration and crust formation
- Infiltrate of medium-sized to large mononuclear cells with indented or grooved nuclei, typical of Langerhans' cells
- Clusters of cells present in papillae and scattered in the upper dermis
- Eosinophils also present
- Immunohistochemical analysis : (+) for CD1a and S-100
- Histologic differential diagnosis : dendritic-cell sarcoma (indeterminate-cell histiocytosis), xanthogranuloma, xanthoma disseminatum, benign cephalic histiocytosis, and occasionally mycosis fungoides (in cases of MF with numerous eo and histiocytes)
- Characteristic morphologic features of Langerhans' cells and, most important, positive staining for CD1

- The diagnosis:  
Cutaneous Langerhans'-cell histiocytosis



- No histologic or immunophenotypic features permit distinction between the two clinical forms of Langerhans'-cell histiocytosis involving the skin

Differential diagnosis in this case :

single-organ–system cutaneous Langerhans'-cell histiocytosis, also known as cutaneous self-healing Langerhans'-cell histiocytosis, and  
multisystem Langerhans'-cell histiocytosis, also known as Letterer–Siwe disease



- Prognosis and treatment vary markedly depending on involvement of other organs
- Prognosis of truly isolated cutaneous single-organ–system Langerhans'-cell histiocytosis is excellent, and observation without treatment is justified
- However, multiorgan-system Langerhans'-cell histiocytosis, particularly in neonates, with involvement of the liver, spleen, lung, the hematopoietic system, or a combination of these is a potentially fatal disease
- In addition, congenital cutaneous single-organ–system Langerhans'- cell histiocytosis not infrequently evolves into multiorgan-system Langerhans'-cell histiocytosis.





- 5-year survival rate of neonates with single-organ–system Langerhans'- cell histiocytosis (most of whom did not receive treatment) was 94%, whereas in multiorgan-system Langerhans'- cell histiocytosis(all of whom were treated) 57%
- Evaluation for the presence of disease in locations other than the skin.

A skeletal survey, CT and MRI of the abdomen confirmed that the size of the liver was at the upper limit of normal and that there was no splenomegaly or intrasplenic lesions



- All skin lesions resolved by 1 month of age
- Median time to regression in retrospective studies of only small numbers of patients is about 4 months. However, relapse with subsequent dissemination to multiorgan-system Langerhans'- cell histiocytosis has been described
- Isolated lesions of the pituitary, including diabetes insipidus — a classic manifestation of Langerhans'-cell histiocytosis — and other neurodegenerative lesions detected in such patients many years after the initial diagnosis
- Followed closely during the first year of life and will continue long-term follow- up at longer intervals.  
At 1 year of age, no evidence of either cutaneous or systemic disease

